SUMMARY MINUTES

OF THE

NEUROLOGICAL DEVICES

ADVISORY PANEL MEETING

3614

OPEN SESSION

May 11, 2000

Conference Room 020B
9200 Corporate Boulevard
Rockville, MD

Neurological Devices Advisory Panel Roster
May 11, 2000

Cedric F. Walker, Ph.D., P.E.
Acting Chairperson

Alexa I. Canady, M.D.
Chairperson, participating by telephone

Richard G. Fessler, M.D., Ph.D.
Voting Member, unable to attend

Robert W. Hurst, M.D.
Voting Member

Gail L Rosseau, M.D.
Voting Member

Constantine A. Gatsonis, Ph.D.
Consultant, Deputized to Vote, participating by telephone

David T. MacLaughlin, Ph.D.
General and Plastic Surgery Devices Panel
Consultant, Deputized to Vote

Anne C. Roberts, M.D.
Circulatory System Devices Panel
Consultant, Deputized to Vote

Sally L. Mahler, Esq.
Industry Representative

Anne W. Wozner, Ph.D., R.N.
Consumer Representative

FDA Participants

Janet Scudiero, M.S.
Panel Executive Secretary

Celia Witten, M.D., Ph.D.
Director, Division of General, Restorative, and Neurological Devices (DGRND)

Stephen P. Rhodes, M.S.
Chief, Plastic and Reconstructive Surgery Devices Branch (PRSB), DGRND

Peter L. Hudson, Ph.D.
Clinical Reviewer, PRSB, DGRND

Judy Chen, M.S.
Statistical Reviewer, Office of Surveillance and Biostatistics

OPEN SESSION—MAY 11, 2000

Panel Executive Secretary Janet Scudiero called the meeting to order at 8:56. a.m., noting that Panel Chairperson Dr. Alexa I. Canady was absent because of travel-related complications and would be participating by telephone. Ms. Scudiero read an appointment to Acting Chairperson for Dr. Cedric Walker and appointments to temporary voting member status for Drs. Gatsonis, MacLaughlin, and Roberts. Dr. Gatsonis was also absent because of weather-related complications and would participate by telephone. Dr. Fessler also was absent due to weather-related complications. Ms. Scudiero read the conflict of interest statement, noting that waivers had been granted to Drs. Fessler and Gatsonis for their interest in firms at issue; these waivers allowed their full participation. Matters involving Drs. Hurst, Gatsonis, and Roberts had been considered but deemed unrelated to the topic at hand, and their full participation was allowed.

Acting Panel Chairperson Dr. Cedric Walker stated that the panel was to consider a premarket approval application (PMA) P990040 for the Cordis Endovascular System (CES), Inc. Trufill n-Butyl Cyanoacrylate and Tantalum Powder intended for the presurgical treatment of arteriovenous malformations (AVMs). He noted that the panel members present constituted a quorum and asked the panel members to introduce themselves.

PANEL UPDATE

Mr. Stephen P. Rhodes, Chief , PRSB updated the panel on topics of the two previous meetings. He noted that in September 1999 the panel recommended that human dura be classified into class II and commented on a guidance document for processing

human dura mater. Since then, the FDA has been considering information provided by the panel and manufacturers as it prepares a classification regulation for human dura matter as a class II device. The panel also provided comment on two draft guidance documents, one for dura substitute devices and one for neurological embolization devices, both of which are in the process of being revised and released. In addition, the panel recommended reclassifying the totally implanted spinal cord stimulator intended for treatment of chronic pain of trunk and limbs from class III into class II. FDA is now evaluating the panel's recommendation, the sponsor's petition and other comments on the proposed reclassification.

Mr. Rhodes stated that at the March 31, 2000 meeting, the panel recommended approval with conditions for the Medtronic Activa System for treatment of Parkinson's disease PMA supplement, a recommendation that FDA is now evaluating.

OPEN PUBLIC HEARING

There were no requests to address the panel.

OPEN COMMITTEE DISCUSSION—CORDIS ENDOVASCULAR SYSTEM INC.'S PMA 990040 FOR THE TRUFILL N-BUTYL CYANOACRYLATE AND TANTALUM POWDER

Sponsor Presentation

Ms. Alina Caraballo, Regulatory Affairs Manager of CES, introduced the PMA and the sponsor representatives.

Dr. Steve Rowlands, Vice President of Research and Development at CES, gave an overview of the device, noting that Trufill device was a liquid embolic agent consisting of n-butyl cyanoacrylate (n-BCA) monomer, tantalum powder, and ethiodized

oil. He read the proposed indications for use, stating that the device is indicated for the embolization of AVMs when presurgical devascularization is desired and that its long-term implant safety and efficacy has not been established.

He described the three device components and gave an overview of how the product is used. Dr. Rowlands described the *in vitro* testing on n-BCA and tantalum powder, which included polymerization rate, sterility, packaging and shelf life, biocompatibility, hydrolytic degradation, elution studies, and catheter compatibility. He noted that the FDA had requested additional testing, which has been initiated but has not been completed and submitted to FDA yet.

Dr. Phillip Purdy, Study Investigator, gave an overview of cerebral AVMs, stressing the very low incidence of AVMs and listing the symptoms that manifest themselves. He noted that because of the rarity of this condition, it was difficult to find enough patients for the clinical trial. He discussed the role of embolization in the treatment of AVMs and listed the goals of preoperative embolization. Dr. Purdy discussed advantages and disadvantages of currently approved embolic materials, such as polyvinyl alcohol (PVA) particles and platinum wire coils. He noted that n-BCA has been used off-label since the 1980s for AVM embolization in the United States and elsewhere using an oil-based contrast and/or tantalum. Dr. Purdy analyzed the variability in size and location of AVMs, stressing their highly variable nature, and showed case examples.

Dr. Thomas Tomsick, Principal Investigator for the study, reported the randomized trial results. The trial was begun in 1996, stopped because of low enrollment, and reinitiated at physician request because of need for the device. The prospective, multi-center, single-blind study had 104 patients randomized to nBCA or

PVA treatment prior to planned microsurgical therapy. It was designed to verify that the device is as safe and effective as conventional treatment for AVMs when preoperative embolization is desired. The primary efficacy endpoint was the degree of vascular occlusion measured by the percentage of AVM nidus obliterated and the number of feeding pedicles embolized, with secondary efficacy endpoints of comparable surgical resection time and surgical blood loss. Primary safety outcomes included the incidence of device and procedure complications and intracranial events and overall neurologic outcome. Dr. Tomsick described the study flow chart and demographics, as well as AVM characteristics and disposition of patients in device and control groups.

Dr. Tomsick presented comparable statistics on the percentage of reduction in AVM volume by stage, patient, and number of vessels occluded for both device and control groups. He reported secondary outcomes in terms of 95 % confidence intervals. The fluoroscopy time, total surgical resection time, blood replacement units, and volume fluid all were also comparable. He listed the coils and particle sizes used, catheters used, and guidewires used for both device and the control groups. Complications were categorized into device- and procedural-related complications. There were more procedural-related complications in the investigational device group and more device-related complications in the control group. Dr. Tomsick analyzed all device-related complications versus adverse clinical outcomes, looking at intracranial events, hemorrhages, and neurological outcome rates. He analyzed the five deaths that occurred during the study, only one of which was in the device group and concluded that the device was equivalent to the PVA control in achieving primary and secondary efficacy endpoints and comparable in clinical safety endpoints.

Ms. Lisa Wells, Senior Manager for Clinical and Regulatory Affairs at CES, gave an overview of the training program. It is covers the use of device, case studies, and a hands-on workshop. She described the course objectives and faculty and gave details on the didactic, hands-on workshop, and review sessions.

Questions from the panel to the sponsors concerned statistical issues, such as confidence limits and power computation, the source of the ethiodized oil, and entry and exit criteria for the training course, as well as why some study patients were not resected during the protocol.

FDA Presentation

Dr. Peter Hudson introduced the FDA review team and read the proposed indications for device use. He described the device and observed that no ratio of the three components was specified in the investigation. He asked the panel to comment on the variable ratios of 10 to 70 % n-BCA and of 30 to 80% ethiodized oil. He also asked that panel to comment on training procedures for using the device.

Dr. Hudson presented preclinical data on the device's chemistry and toxicology/biocompatibility, describing the chemical characteristics of n-BCA, tantalum, and ethiodized oil. He stated that because ethiodized oil and tantalum may be released from the polymerized device *in situ* over time, the FDA had requested experiments to determine how much ethiodized oil and tantalum elutes from the device during its use. He also discussed polymerization and catheter compatibility. Dr. Hudson stated that the n-BCA and tantalum biocompatibility/toxicology test results were all acceptable, but there was no subchronic/chronic testing data available on either substance other than post-

implantation studies at 7 and 30 days. There were also no biocompatibility/toxicology data on the combined device components.

Dr. Hudson described the clinical study design and listed inclusion and exclusion criteria. He explained the sample size justification for bioequivalence, noting that clinical tolerance for the study was defined as 20%. He listed the primary and secondary efficacy endpoints and discussed patient accounting and demographics. Primary efficacy results were similar in vessels occluded but better in the control group for percent reduction in lesion volume. Secondary results were similar in time of resection and favored investigational device for number of transfusions required. On safety results, Dr. Hudson showed statistics on device and procedural complications for both groups, noting some discrepancies on counting methods and terminology.

Judy Chen, FDA statistician, gave the statistical review, noting that the study was designed to show device equivalence by comparing 52 patients treated with device to 52 treated with control PVA particles. She noted two ambiguities: a lack of clear definition of the device components in the mixing ratios and a change in the primary effectiveness endpoint from the proportion of successes to the percentage of reduction of lesion volume. She questioned whether the tolerable difference of 20% is clinically acceptable and whether the sample size was large enough. On effectiveness, she observed that an analysis of covariance shows no statistically significant treatment difference in the percentage of lesion volume resection or the number of occluded vessels, but questioned whether equivalence can be determined solely on nonstatistically significant findings. A finding of no statistically significant difference can be due to small sample size, poor study performance, or lack of accuracy in measuring the endpoint. Therefore, she looked

at equivalence evaluation via confidence limits, which showed a mean difference of 18.5% at the 95% upper limit in favor of control. She concluded by asking whether the safety and effectiveness of the device can be determined when the mixing ratio is variable, when a high proportion of ratio data are missing, and whether the prespecified tolerable treatment difference of 20% is applicable to the difference in lesion volume reduction.

Questions from the panel to the FDA concerned whether the device-related complications produced adverse clinical outcomes and how the counting methods were applied to device versus procedural-related events.

Panel Preclinical Review

Dr. David MacLaughlin reviewed the preclinical studies, which he saw as related to manufacture and storage, performance, and safety/toxicity of the device. He noted that sensitization, irritation, systemic toxicity, and cytotoxicity were adequately addressed. He stated that there were unresolved issues relating to the device identification, to subsequent testing on the combined device components rather than just its components, and short- and long-term safety measures of the device *in situ*. His specific concern was that the sponsor should define the composition of the device more clearly or provide an algorithm for its use. Because the device is really a series of devices composed of one, two, or three components, in varying ratios depending upon clinical judgement, he recommended defining a range of ratios that are effective at embolization and safe. He also observed that *in vivo* biocompatibility testing to date did not address the long-term safety issue that some AVMs embolized with the device are not surgically removed. He recommended the following safety testing on clinically-used device

component ratios: acute biocompatibility, leaching of components, mammalian/bacterial cell mutagenesis, device hydrolytic products, and long-term *in vivo* testing. He concluded that preclinical testing provides important information about the safety of the individual components of the device. He believes that this testing should be completed on a more reasonable representation of the clinical device.

Industry Representative Sally Maher, Esq., commented that the burden of long-term testing was unfair to the sponsor, because this involved off-label use.

Panel Clinical Review

Dr. Robert Hurst stressed that when dealing with brain AVMs, it is important to view treatment options in clinical perspective. He reviewed the history of the PMA, stressing the rarity, heterogeneous nature, and variable pathophysiology of AVMs and the widely varying risks of treatment that make it difficult to collect large homogeneous groups of patients for study. He also stressed the devastating effects of AVMs and the clinical imperative for treatment. He concluded that the PMA indicates very satisfactory performance of the device in comparison with currently approved treatment on the percent of occlusion of AVMs, the number of occluded vessels, the number of procedure-related complications, and the number of intracranial complications. He added that the clinical study was restarted because of pressure from the physicians involved in the study because U.S. physicians lacked access to this device, which has become the standard of care in brain AVM treatment throughout most of the world since the 1970s. He found that the PMA data indicate very satisfactory performance in clinical efficacy and safety of cyanoacrylate, which is at least equivalent to the currently available embolic agent. He concluded by stating that the majority of experts in the field believe that there is a need

for FDA approval of this device to make the most effective treatment for brain AVMs available in the U. S.

Panel Statistical Review

Dr. Constantine Gatsonis listed several technical questions in his review: whether the bootstrapping analysis was done for the full model or just the response data, the rationale for the equivalence threshold, and the rationale for the power calculations used in the study. He noted that with so few patients in each arm of the study, even though the confidence intervals are large, one could not conclude whether there is a difference between the two modalities. He expressed doubt that the two procedures had clearly demonstrated equivalence.

Sponsor statistical consultant Hoi Leung replied that the bootstrap analysis was performed on the response data only and that the 20% threshold, while a clinical issue, has often been used. He explained the basis for the power calculation and stated that the confidence interval was high to provide maximum confidence with inevitably small sample sizes.

Industry Representative Sally Maher, Esq., stressed that the goal of the PMA was to provide reasonable assurance of device safety and efficacy rather than to demonstrate equivalence.

Other panel comments involved the use of particular catheters in tortuous veins.

FDA Questions to the Panel

There was consensus among the panel that specific guidelines on appropriate component ratios for a given anatomic site are difficult to quantify and that the sponsor-provided recommendations are adequate. The fact that the amount of n-BCA used varied

from 10% to 70% in the efficacy study should be stated in the labeling, but the panel stressed it was important to give clinicians the latitude necessary for treatment. The panel also thought the sponsor-provided training was adequate but suggested that the sponsor might wish to consider entry criteria and a periodic review course. They noted that it is a good policy to sell the device only to hospitals with trained personnel. The panel did not suggest any further preclinical or clinical studies to define the component ratios.

On long-term implantation, the panel recommended that labeling should emphasize that the device is a product for presurgical use only. Long-term use is impossible to predict, although the panel acknowledged that such use is possible. There was some panel concern that the product could be used long-term, albeit such use is inconsistent with the labeling, so perhaps sponsors should consider long-term effects.

There was general but not unanimous agreement that the device is effective. There was a panel consensus that the 20% clinical tolerance is adequate, although there was some opinion that the changed endpoint is a statistical problem. Nonetheless, the fact that the original terminated study was restarted at physicians' request should be considered.

On safety, the panel observed that while complications were noted, they did not represent a danger to the patient or an unsafe device. It was suggested that it would have been more appropriate to analyze device-related complications versus patient complications or procedural complications and intracranial events. It was also noted that some complications were related to the catheter delivery system rather than to the device itself.

OPEN PUBLIC HEARING

There were no requests to address the panel.

FDA and Sponsor Remarks

FDA and sponsor representatives thanked the panel for their consideration.

Panel Recommendation and Vote

Panel Executive Secretary Ms. Scudiero read the panel voting options.

A motion to recommend the PMA as approvable failed for lack of a second.

A motion to recommend the PMA as approvable with conditions was made and seconded. The conditions were as follows:

1) Labeling should be amended to note that long-term biocompatibility was not studied.
2) Labeling should specify that the preclinical studies were done only with a range of 10 to 70% n-BCA.
3) Completion of the physician training program should be required prior to allowing a physician to use the device.
4) The results of ongoing studies of the combined components of the device should be submitted to FDA, and these results should be as acceptable as the previous test results for the individual device components.

(An amendment recommending that data be included in the labeling on the combined device for the 10-70% extremes of dose response failed for lack of a second.)

The motion to recommend the PMA as approvable subject to the above four conditions passed. Those who voted in favor of the motion stated that they found the evidence for safety and efficacy convincing, and that the device provided an important solution for a difficult problem. Dr. Roberts added that long-term chronic toxicity testing would be important in the future. Drs. Gatsonis and MacLaughin voted against the

motion because of the incomplete preclinical testing on the device and the lack of convincing methodology and results.

Dr. Celia Witten thanked the panel and participants on behalf of the FDA.

Dr. Walker thanked the panel and all presenters. He adjourned the day's session at 2:05 p.m.

I certify that I attended the Open Session of the Neurological Devices Advisory Panel Meeting on May 11, 2000, and that this summary accurately reflects what transpired.

Janet L. Scudiero, 7/12/00

Janet L. Scudiero, M.S.
Panel Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

Cedric F. Walker, Ph.D., P.E.
Acting Panel Chairperson

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Summary minutes revised by
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